REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claims 43-45 and 53-56 were rejected under 35 USC § 112, first paragraph, as claiming new matter. In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

At the outset, Applicants note that the statement of the rejection also lists claims 17-19, 24, 25, 28-30, 32-41, 46, 48, 57 and 58. However, these claims depend on claim 17 and the Examiner says in the next-to-last paragraph on page 3 of the Office Action that the rejection of claim 17 has been withdrawn. Accordingly, the continued reference to claims 17-19, 24, 25, 28-30, 32-41, 46, 48, 57 and 58 is believed to be in error.

Claims 53-55 have been canceled without prejudice.

Concerning claim 56, Applicants respectfully point out that the support for step (b) is not only p. 9, last three lines, but also original claim 7, notably step (a2), which refers to a donor DNA that comprises the same two mutually incompatible first RRS contained in the acceptor DNA and further specifying it by reference to a recombination vector as defined in claims 2-4. Applicants respectfully submit that this clearly serves as a basis for the feature that the RRS in the acceptor DNA and the functional DNA sequence are identical.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claims 17-19, 24, 25, 28-30, 32-46 and 53-58 were rejected under 35 USC § 112, second paragraph, as being indefinite. In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well.

With respect to claim 17, and specifically the phrase "a modified Rosa26 locus," Applicants respectfully submit that the Rosa26 locus defines a certain stretch of nucleotides on the chromosome as acknowledged by the Examiner. It is, however, readily apparent to persons skilled in the art that such stretch of nucleotides can be modified, e.g., by introduction of an integration cassette. Thus, the objected term thus has a clear defined meaning for a person skilled in the art. Similarly the wording "promoter heterologous to the Rosa26 locus" has a clear meaning for a skilled person; it defines the promoter sequence of the above-mentioned stretch of nucleotides as being one that is not endogenous to the Rosa26 locus. In this regard, Applicants note further that terms are not to be read in a vacuum, but in the context of the specification to which the claims are a part. *In re Moore et al.,* 169 USPQ 236, 238 (CCPA 1971). The teaching of the instant specification, particularly in the first paragraph on page 8, makes clear what Applicants intend as the scope of the heterologous promoter. If the Examiner has alternative language he prefers, Applicants respectfully request that the Examiner indicate this.

With respect to claim 32, concerning the objections of the Examiner with regard to the term "inducible tissue specific promoter" and "inducible ubiquitous promoter," Applicants respectfully submit that these terms also have a clear meaning to persons skilled in the art. A

person skilled in the art would undoubtedly understand that the objected terms refer to tissue-specific promoters and ubiquitous promoters, respectively, which by use of specific inducer sequences can be rendered inducible. A person skilled in the art would know which kind of inducer sequences are required or have to be present in order to render a given promoter an inducible promoter. Consequently, once again, Applicants perceive no indefiniteness. Again, if the Examiner has alternative language he prefers, Applicants respectfully request that the Examiner indicate this.

With respect to claim 33, Applicants have provided the full terminology along with the abbreviations as requested by the Examiner.

With respect to claim 45, and the objection to the term "inactive positive selection marker," Applicants respectfully point out that the article of Fukushige at ID, 7905, left column, last paragraph refers to an inactive lox-neo-fusion gene that is integrated by cre-mediated integration yielding a functional ATG-Iox neofusion gene in the cell. Thus, Applicants respectfully submit that the objectionable wording has a clear meaning to persons skilled in the art.

Claim 55 has been canceled, thereby mooting this rejection as to that claim.

Finally, with respect to claim 56, Applicants point out that the term “mutually incompatible RRS” mentioned in claim 56 is defined in Schlake T. and Bode J. (1994), Use of mutated FLP recognition target (FRT) sites for the exchange of expression cassettes at defined chromosomal loci. Biochemistry 33, 12746-12751. A copy of the Schlake reference will be filed shortly.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claims 17-25, 28-30, 32, 34-38, 43-46, 48 and 53-56 were rejected under 35 USC § 102(b) as being anticipated by Soriano et al. ("Soriano"), WO99/53017. In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well. First of all, Applicants note that the lacZ gene, which corresponds to the target gene in the present application, is introduced in the Rosa26 transgenic mouse in Soriano to be under control of the homologous Rosa26 promoter (detector construct). Second, the embodiment shown in Figs. 1C and 4 refers to a reporter cassette comprising a neo-reporter gene and a polyadenylation cassette under the control of a heterologous PGK promoter. The reporter cassette is integrated into the detector cassette and then integrated into the Rosa26 locus (see legends to Fig. 1 and Examples of Soriano). Thus, the Rosa26 product thus obtained in Soriano has a target protein (here lacZ), which is under the control of the ***endogenous*** Rosa promoter, and a marker peptide of neo which is under control of the heterologous promoter. This is clearly different from the construct required by the instant claims where the functional DNA sequence comprises a selectable marker and a gene of interest and wherein the gene of interest is under the control of a promoter ***heterologous*** to the Rosa26 locus. Further, according to the present application the target protein is not a selectable marker gene. Thus, Soriano cannot anticipate the claimed subject matter.

Moreover, Applicants respectfully submit that the claimed configuration of the integration vector was not obvious in view of Soriano. There was, at the time the present invention was made, no motivation to use a promoter heterologous to the Rosa26 locus promoter instead of the endogenous Rosa26 promoter. The configuration of the present application also

provides for unexpected properties as the expression with promoters that are heterologous to the Rosa26 locus provides for expression patterns different from that of the Rosa26 locus promoter. In other words, the method of the present application is not limited to the Rosa26 expression pattern as is Soriano. The claimed subject matter, thus, also encompasses an inventive step.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
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